REMARKS

The claims have been amended to clarify the invention. Claim 2 has been amended to recite the claimed polynucleotide sequences in consisting of language, and claim 3 has been amended to delete the phrase "biologically active". No new matter is added by these amendments, and entry of the amendments is requested.

Rejections/Objections Withdrawn

The objections and rejections made in Paper No. 8 are withdrawn in view of applicant's amendments and arguments thereto.

New Objections/Rejections

Claim Objections

The Examiner has objected to claim 2 under 37 CFR 1.75(c) as being of improper dependent form for failing to further limit the subject matter of a previous claim. Claim 2 recites an antigenic epitope of claim 1 comprising residues 550-565 of SEQ ID NO:4. Due to its open language, claim 2 reads on antigenic epitope comprising SEQ ID NO:4 since SEQ ID NO:4 "comprises" residues 550-565. The Examiner stated that the objection can be obviated by amending the claims to an antigenic epitope of the protein of claim 1 consisting of residues 550-565.

Claim 2 has been so amended and withdrawal of the objection is therefore requested.

35 U.S.C. § 112, First Paragraph, Rejection of Claims 1-4

The Examiner has rejected claims 1-4 under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contain subject matter which is not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The Examiner recited factors to be considered in determining whether undue experimentation is required as summarized inn *Ex parte* Forman. The claims are drawn to a purified protein comprising an amino acid sequence of SEQ ID NO:4, and antigenic epitope of the protein of claim 1 and a biologically active portion of the protein of claim 1. However, the Examiner stated, the specification fails to enable any person of skill in the art to use the claimed protein in any predictable manner either

for diagnostic or therapeutic purposes. The Examiner stated that the inventors have asserted that the polynucleotide (SEQ ID NO:3) *encoding* the protein of SEQ ID NO:4 is a "tumor suppressor gene". That differential expression of SEQ ID NO:3 in ovary tumor cells compared to normal ovary cells revealed a lower fractional abundance of SEQ ID NO:3. Further, that via transcript imaging, SEQ ID NO:3 is diagnostic of prostate cancer, ovarian cancer, and pancreatic cancer.

The Examiner stated however, that those of skill in the art recognize that expression of mRNA, specific for a tissue type, does not necessarily correlate or predict proportionate levels of polypeptide translation. The Examiner then cited various publications in support of this allegation. See, in particular, Alberts et al., Fu et al., and Rama et al. cited at pages 4-5 of the Office Action. The Examiner concluded that thus, the predictability of protein translation and its possible use as a diagnostic are not contingent on the levels of mRNA expression due to a multitude of homeostatic factors affecting transcription and translation. The Examiner stated further that for "an antibody which specifically binds the protein" to serve as a clinically relevant diagnostic marker for cancer, the claimed protein must be present only in cancer tissue to the exclusion of normal tissue (or vice versa).

Further, the Examiner stated, with regards to the use of the protein in treating cancer, the specification fails to provide sufficient guidance and or objective evidence to one of skill in the art tha the protein will predictably function as a therapeutic. The Examiner then cited various publication alleging to support his position that the treatment of cancer is at most unpredictable. See, in particular, Gura and Bellone et al., cited at page 6 of the Office Action. The Examiner concluded, therefore, that it would require undue experimentation by one of skill in the art to use the invention as claimed.

Applicants Response

Claim 2 has been amended to delete the phrase "biologically active". Applicant first of all note that the Examiner has not refuted applicants assertions for both a well established utility for the claimed protein, or for antibodies to the claimed protein, in toxicology testing and drug discovery, as well as a specific and substantial utility in the diagnosis of cancers of the breast, ovary, prostate, and pancreas based on differential expression data in ovarian, prostate, and breast cancer cells relative to normal tissues cells (table at page 12), and Northern analysis (pages 35-37). In fact, the Examiner has withdrawn the rejection under 35 U.S.C. § 101, based on applicants amendments and arguments to this rejection (see Office Action, page 2). For this reason alone, the skilled artisan would clearly know

how to use the claimed invention in toxicology testing and drug discovery, and in the detection and diagnosis of various cancers.

Nevertheless, applicants disagree with the Examiner's allegation that mRNA expression does not correlate with or predict polypeptide expression in the instant case.

Regulation of gene expression occurs at many levels, including transcription, splicing, polyadenylation, mRNA stability, mRNA transport and compartmentalization, translation efficiency, protein modification and protein turnover. While steady state mRNA levels are not always directly proportional to the amount of protein produced in a cell, mRNA levels are **routinely** used as an indicator of protein expression. Countless scientific publication have been based on data relating to mRNA levels when the polypeptide encoded by the mRNA was unknown or difficult to detect. Moreover, mRNA levels are **usually** a good indicator of protein levels in a cell. The Office Action cites three examples of protein regulation downstream of transcription; however, these examples represent comparatively unusual mechanisms of gene regulation. According to B. Lewin [(1997) Genes VI Oxford University Press, Inc. New York, NY] (pages attached as Exhibit A):

> Transcription of a gene in the active state is controlled at the stage of initiation, that is, by the interaction of RNA polymerase with its promoter. This is now becoming susceptible to study in the *in vitro* systems... ***For most genes, this is a major control point; probably it is the most common level of regulation.*** [page 847, emphasis added].
>
> But having acknowledged that control of gene expression can occur at multiple stages, and that production of RNA cannot inevitably be equated with production of protein, it is clear that ***the overwhelming majority of regulatory events occur at the initiation o transcription. Regulation of tissue-specific gene transcription lies at the heart of eukaryotic differentiation.*** [pages 847-848, emphasis added]

Thus the question is not whether there is the potential for post-transcriptional regulation of SEQ ID NO:4 expression but whether one skilled in the art would have a reasonable expectation that SEQ ID NO:4 expression correlates with the levels of SEQ ID NO:3 mRNA. Applicants need only prove a "substantial likelihood" of utility and hence of enablement; certainty is not required. *Brenner v. Manson*, 383 U.S. 519, 532, 148 USPQ 689 (1966). In the case of the instant invention, one skilled in the art would be imprudent in assuming, *a priori*, that protein levels did not correspond to mRNA levels and that levels of SEQ ID NO:4 were controlled predominantly in a post-transcriptional manner,

thereby dismissing the significance of mRNA levels.

Appellants respectfully reiterate the assertion that mRNA levels are usually a good indicator of protein levels. This suggests that the regulation of genes is at the level of transcription. While there are examples in the literature of genes that are regulated post-transcriptionally, the authoritative text in the field of molecular biology, Alberts et al.;*The Molecular Biology of the Cell*, which the Examiner has cited in support of his allegtion, as well as a wealth of data in the literature indicate that the *predominant* level of control of gene expression is at transcription. For example, in discussing the complicated process of gene expression, Alberts et al. state,

> There are many steps in the pathway leading from DNA to protein, and all of them can in principle be regulated. Thus a cell can control the proteins it makes by (1) controlling when and how often a given gene is transcribed (transcriptional control), (2) controlling how the primary RNA transcript is spliced or otherwise processed (RNA processing control), (3) selecting which completed mRNAs in the cell nucleus are exported to the cytoplasm (RNA transport control), (4) selecting which mRNAs in the cytoplasm are translated by ribosomes (translational control), (5) selectively destabilizing certain mRNA molecules in the cytoplasm (mRNA degradation control), or (6) selectively activating, inactivating or compartmentalizing specific protein molecules after they have been made (protein activity control).
>
> **For most genes transcriptional controls are paramount**...Although all of the steps involved in expressing a gene can in principle be regulated, for most genes the initiation of RNA transcription is the most important point of control." (emphasis added).
> (*The Molecular Biology of the Cell*, Alberts B. et al., editors, Garland Publishing, Inc., 1994, 3rd Edition, page 403-404; Exhibit B).

Even in discussing posttranscriptional controls, Alberts et al. state that, "[a]lthough controls on the initiation of gene transcription are the predominant form of regulation for most genes, other controls can act later in the pathway from RNA to protein to modulate the amount of gene product that is made" (Alberts et al., page 453, Exhibit C). Indeed Alberts et al. goes on to describe several examples of genes exhibiting posttranscriptional control, including the example cited by the Examiner at page 465 of the Alberts reference. However, the fact that there are examples of genes that are regulated by posttranscriptional controls, does not detract from the observation that the *preponderance* of genes are regulated at the level of transcription. This, therefore supports Appellants' assertion that mRNA levels are *usually* a good indicator of protein levels, as in the instant case absent evidence to the contrary.

Furthermore, applicants disagree that for the claimed protein to "serve as a clinically relevant diagnostic marker for cancer" the claimed protein must be present in cancer tissue to the exclusion of

normal tissue or vise versa. As the Examiner has acknowledged, applicants have shown at page 12 of the specification, lines 17-30, that differential expression of the polynucleotide encoding the claimed protein (and hence the claimed protein) in cancerous ovary tissue matched with corresponding normal tissue from the same donor is sufficient to indicate the presence of cancer and therefore does not require the complete exclusion of the marker in one tissue versus the other.

Applicants therefore submit that for all the above reasons, as well as those given previously in the response filed 6/16/2003, the specification discloses both well established and specific and substantial asserted utilities for the claimed protein of SEQ ID NO:4, as well as for fragments of the claimed protein in the making of antbodies to detect the claimed protein, and that the skilled artisan would clearly know how to use them for these purposes. Withdrawal of the rejection of claims 1-4 under 35 U.S.C. § 112, first paragraph is therefore requested.

CONCLUSION

In light of the above amendments and remarks, Applicants submit that the present application is fully in condition for allowance, and request that the Examiner withdraw the outstanding objections/rejections. Early notice to that effect is earnestly solicited. Applicants further request that, upon allowance of claim 1, claims 5-8 be rejoined and examined as methods of use of the polypeptides of claim 1 that depend from and are of the same scope a claim 1 in accordance with *In re Ochiai* and the MPEP § 821.04.

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, Applicants invite the Examiner to contact the undersigned at the number listed below.

Applicants believe that no fee is due with this communication. However, if the USPTO determines that a fee is due, the Commissioner is hereby authorized to charge Deposit Account No. **09-0108.**

Respectfully submitted,

INCYTE CORPORATION

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Attachment(s):

1) B. Lewin (1997) Genes VI Oxford University Press, Inc. New York, NY, pages 847-848; Exhibit A
2) Alberts et al. (1994) Molecular Biology of The Cell, 3rd Edition, Garland Publishing, Inc., New York & London, pages 403-404; Exhibit B
3) Alberts et al., *ibid,* page 453; Exhibit C

GENES VI

Benjamin Lewin

Oxford New York Tokyo
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Oxford New York
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CHAPTER 29

Regulation of transcription

The phenotypic differences that distinguish the various kinds of cells in a higher eukaryote are largely due to differences in the expression of genes that code for proteins, that is, those transcribed by RNA polymerase II. In principle, the expression of these genes might be regulated at any one of several stages. The concept of the "level of control" implies that gene expression is not necessarily an automatic process once it has begun. It could be regulated in a gene-specific way at any one of several sequential steps. We can distinguish (at least) five potential control points, forming the series:

Activation of gene structure
↓
Initiation of transcription
↓
Processing the transcript
↓
Transport to cytoplasm
↓
Translation of mRNA

The existence of the first step is implied by the discovery that genes may exist in either of two structural conditions. Relative to the state of most of the genome, genes are found in an "active" state in the cells in which they are expressed (see Chapter 27). The change of structure is distinct from the act of transcription, and indicates that the gene is "transcribable." This suggests that acquisition of the "active" structure must be the first step in gene expression.

Transcription of a gene in the active state is controlled at the stage of initiation, that is, by the interaction of RNA polymerase with its promoter. This is now becoming susceptible to analysis in the *in vitro* systems (see Chapter 28). For most genes, this is a major control point: probably it is the most common level of regulation.

There is at present no evidence for control at subsequent stages of transcription in eukaryotic cells, for example, via antitermination mechanisms.

The primary transcript is modified by capping at the 5′ end, and usually also by polyadenylation at the 3′ end. Introns must be spliced out from the transcripts of interrupted genes. The mature RNA must be exported from the nucleus to the cytoplasm. Regulation of gene expression by selection of sequences at the level of nuclear RNA might involve any or all of these stages, but the one for which we have most evidence concerns changes in splicing: some genes are expressed by means of alternative splicing patterns whose regulation controls the type of protein product (see Chapter 30).

Finally, the translation of an mRNA in the cytoplasm can be specifically controlled. There is little evidence for the employment of this mechanism in adult somatic cells, but it does occur in some embryonic situations, as described in Chapter 7. The mechanism is presumed to involve the blocking of initiation of translation of some mRNAs by specific protein factors.

But having acknowledged that control of gene expression can occur at multiple stages, and that production of RNA cannot inevitably be equated with production of protein, it is clear

that the overwhelming majority of regulatory events occur at the initiation of transcription. Regulation of tissue-specific gene transcription lies at the heart of eukaryotic differentiation; indeed, we see examples in Chapter 38 in which proteins that regulate embryonic development prove to be transcription factors. A regulatory transcription factor serves to provide common control of a large number of target genes, and we seek to answer two questions about this mode of regulation: what identifies the common target genes to the transcription factor; and how is the activity of the transcription factor itself regulated in response to intrinsic or extrinsic signals?

Response elements identify genes under common regulation

The principle that emerges from characterizing groups of genes under common control is that *they share a promoter element that is recognized by a regulatory transcription factor.* An element that causes a gene to respond to such a factor is called a **response element;** examples are the **HSE** (heat shock response element), **GRE** (glucocorticoid response element), **SRE** (serum response element).

The properties of some inducible transcription factors and the elements that they recognize are summarized in **Table 29.1.** Response elements have the same general characteristics as upstream elements of promoters or enhancers. They contain short consensus sequences, and copies of the response elements found in different genes are closely related, but not necessarily identical. The region bound by the factor extends for a short distance on either side of the consensus sequence. In promoters, the elements are not present at fixed distances from the startpoint, but are usually <200 bp upstream of it. The presence of a single element usually is sufficient to confer the regulatory response, but sometimes there are multiple copies.

Table 29.1 Inducible transcription factors bind to response elements that identify groups of promoters or enhancers subject to coordinate control.

Regulatory Agent	Module	Consensus	Factor
Heat shock	HSE	CNNGAANNTCCNNG	HSTF
Glucocorticoid	GRE	TGGTACAAATGTTCT	Receptor
Phorbol ester	TRE	TGACTCA	AP1
Serum	SRE	CCATATTAGG	SRF

Response elements may be located in promoters or in enhancers. Some types of elements are typically found in one rather than the other: usually an HSE is found in a promoter, while a GRE is found in an enhancer. We assume that all response elements function by the same general principle. *A gene is regulated by a sequence at the promoter or enhancer that is recognized by a specific protein. The protein functions as a transcription factor needed for RNA polymerase to initiate. Active protein is available only under conditions when the gene is to be expressed; its absence means that the promoter is not activated by this particular circuit.*

An example of a situation in which many genes are controlled by a single factor is provided by the heat shock response. This is common to a wide range of prokaryotes and eukaryotes and involves multiple controls of gene expression: an increase in temperature turns off transcription of some genes, turns on transcription of the **heat shock genes,** and causes changes in the translation of mRNAs. The control of the heat shock genes illustrates the differences between prokaryotic and eukaryotic modes of control. In bacteria, a new sigma factor is synthesized that directs RNA polymerase holoenzyme to recognize an alter-

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...acts. If these minor cell proteins differ among cells to the same extent as the ...re abundant proteins, as is commonly assumed, only a small number of pro... differences (perhaps several hundred) suffice to create very large differences ...ell morphology and behavior.

A Cell Can Change the Expression of Its Genes in Response to External Signals [3]

Most of the specialized cells in a multicellular organism are capable of altering their patterns of gene expression in response to extracellular cues. If a liver cell is exposed to a glucocorticoid hormone, for example, the production of several specific proteins is dramatically increased. Glucocorticoids are released during periods of starvation or intense exercise and signal the liver to increase the production of glucose from amino acids and other small molecules; the set of proteins whose production is induced includes enzymes such as tyrosine aminotransferase, which helps to convert tyrosine to glucose. When the hormone is no longer present, the production of these proteins drops to its normal level.

Other cell types respond to glucocorticoids in different ways. In fat cells, for example, the production of tyrosine aminotransferase is reduced, while some other cell types do not respond to glucocorticoids at all. These examples illustrate a general feature of cell specialization—different cell types often respond in different ways to the same extracellular signal. Underlying this specialization are features that do not change, which give each cell type its permanently distinctive character. These features reflect the persistent expression of different sets of genes.

Gene Expression Can Be Regulated at Many of the Steps in the Pathway from DNA to RNA to Protein [4]

If differences between the various cell types of an organism depend on the particular genes that the cells express, at what level is the control of gene expression exercised? There are many steps in the pathway leading from DNA to protein, and all of them can in principle be regulated. Thus a cell can control the proteins it makes by (1) controlling when and how often a given gene is transcribed (**transcriptional control**), (2) controlling how the primary RNA transcript is spliced or otherwise processed (**RNA processing control**), (3) selecting which completed mRNAs in the cell nucleus are exported to the cytoplasm (**RNA transport control**), (4) selecting which mRNAs in the cytoplasm are translated by ribosomes (**translational control**), (5) selectively destabilizing certain mRNA molecules in the cytoplasm (**mRNA degradation control**), or (6) selectively activating, inactivating, or compartmentalizing specific protein molecules after they have been made (**protein activity control**) (Figure 9–2).

For most genes transcriptional controls are paramount. This makes sense because, of all the possible control points illustrated in Figure 9–2, only transcriptional control ensures that no superfluous intermediates are synthesized. In the

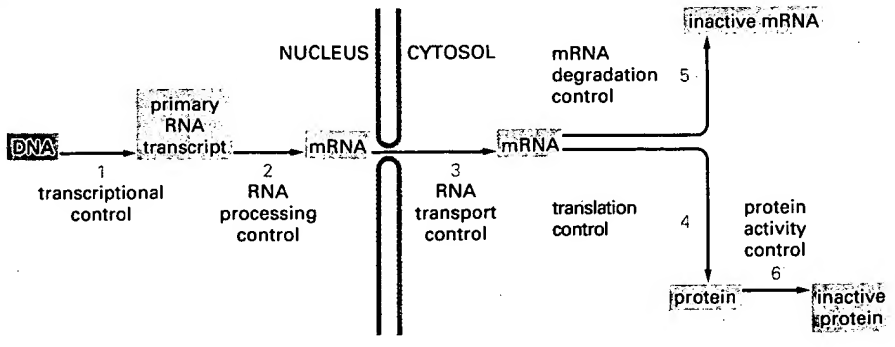

Figure 9–2 **Six steps at which eucaryote gene expression can be controlled.** Only controls that operate at steps 1 through 5 are discussed in this chapter. The regulation of protein activity (step 6) is discussed in Chapter 5; this includes reversible activation or inactivation by protein phosphorylation as well as irreversible inactivation by proteolytic degradation.

following sections we discuss the DNA and protein components that regulate the initiation of gene transcription. We return at the end of the chapter to the other ways of regulating gene expression.

Summary

The genome of a cell contains in its DNA sequence the information to make many thousands of different protein and RNA molecules. A cell typically expresses only a fraction of its genes, and the different types of cells in multicellular organisms arise because different sets of genes are expressed. Moreover, cells can change the pattern of genes they express in response to changes in their environment, such as signals from other cells. Although all of the steps involved in expressing a gene can in principle be regulated, for most genes the initiation of RNA transcription is the most important point of control.

DNA-binding Motifs in Gene Regulatory Proteins [5]

How does a cell determine which of its thousands of genes to transcribe? As discussed in Chapter 8, the transcription of each gene is controlled by a regulatory region of DNA near the site where transcription begins. Some regulatory regions are simple and act as switches that are thrown by a single signal. Other regulatory regions are complex and act as tiny microprocessors, responding to a variety of signals that they interpret and integrate to switch the neighboring gene on or off. Whether complex or simple, these switching devices consist of two fundamental types of components: (1) short stretches of DNA of defined sequence and (2) *gene regulatory proteins* that recognize and bind to them.

We begin our discussion of gene regulatory proteins by describing how these proteins were discovered.

Gene Regulatory Proteins Were Discovered Using Bacterial Genetics [6]

Genetic analyses in bacteria carried out in the 1950s provided the first evidence of the existence of **gene regulatory proteins** that turn specific sets of genes on or off. One of these regulators, the *lambda repressor*, is encoded by a bacterial virus, *bacteriophage lambda*. The repressor shuts off the viral genes that code for the protein components of new virus particles and thereby enables the viral genome to remain a silent passenger in the bacterial chromosome, multiplying with the bacterium when conditions are favorable for bacterial growth (see Figure 6–80). The lambda repressor was among the first gene regulatory proteins to be characterized, and it remains one of the best understood, as we discuss later. Other bacterial regulators respond to nutritional conditions by shutting off genes encoding specific sets of metabolic enzymes when they are not needed. The *lac repressor*, for example, the first of these bacterial proteins to be recognized, turns off the production of the proteins responsible for lactose metabolism when this sugar is absent from the medium.

The first step toward understanding gene regulation was the isolation of mutant strains of bacteria and bacteriophage lambda that were unable to shut off specific sets of genes. It was proposed at the time, and later proved, that most of these mutants were deficient in proteins acting as specific repressors for these sets of genes. Because these proteins, like most gene regulatory proteins, are present in small quantities, it was difficult and time-consuming to isolate them. They were eventually purified by fractionating cell extracts on a series of standard chromatography columns (see pp. 166–169). Once isolated, the proteins were shown to bind to specific DNA sequences close to the genes that they

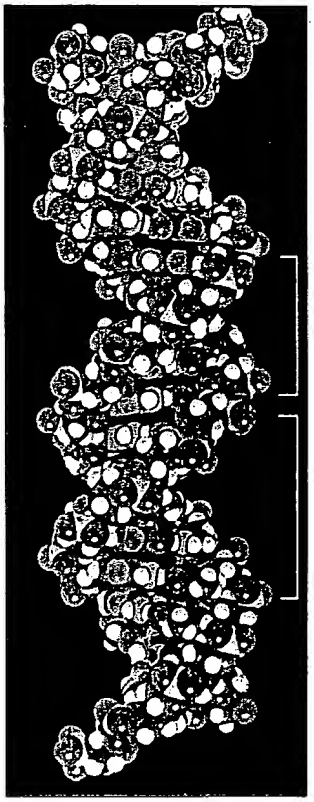

Figure 9–3 **Double-helical structure of DNA.** The major and minor grooves on the outside of the double helix are indicated. The atoms are colored as follows: carbon, *dark blue;* nitrogen, *light blue;* hydrogen, *white;* oxygen, *red;* phosphorus, *yellow.*

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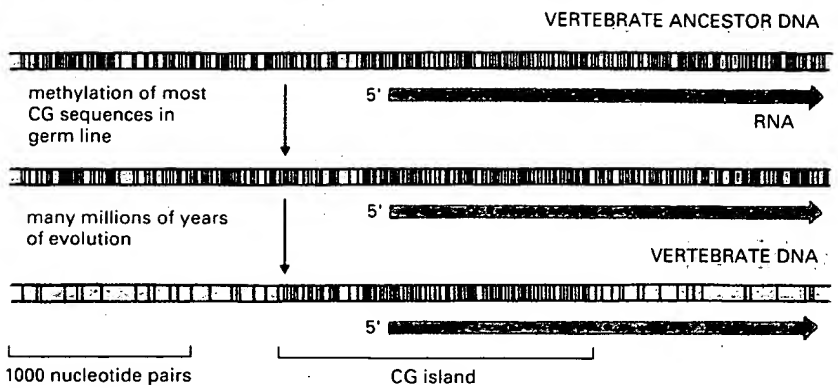

Figure 9–71 **A mechanism to explain both the marked deficiency of CG sequences and the presence of CG islands in vertebrate genomes.** A *black line* marks the location of an unmethylated CG dinucleotide in the DNA sequence, while a *red line* marks the location of a methylated CG dinucleotide.

Summary

The many types of cells in animals and plants are created largely through mechanisms that cause different genes to be transcribed in different cells. Since many specialized animal cells can maintain their unique character when grown in culture, the gene regulatory mechanisms involved in creating them must be stable once established and heritable when the cell divides, endowing the cell with a memory of its developmental history. Procaryotes and yeasts provide unusually accessible model systems in which to study gene regulatory mechanisms, some of which may be relevant to the creation of specialized cell types in higher eucaryotes. One such mechanism involves a competitive interaction between two (or more) gene regulatory proteins, each of which inhibits the synthesis of the other; this can create a flip-flop switch that switches a cell between two alternative patterns of gene expression. Direct or indirect positive feedback loops, which enable gene regulatory proteins to perpetuate their own synthesis, provide a general mechanism for cell memory.

In eucaryotes gene transcription is generally controlled by combinations of gene regulatory proteins. It is thought that each type of cell in a higher eucaryotic organism contains a specific combination of gene regulatory proteins that ensures the expression of only those genes appropriate to that type of cell. A given gene regulatory protein may be expressed in a variety of circumstances and typically is involved in the regulation of many genes.

In addition to diffusible gene regulatory proteins, inherited states of chromatin condensation are also utilized by eucaryotic cells to regulate gene expression. In vertebrates DNA methylation also plays a part, mainly as a device to reinforce decisions about gene expression that are made initially by other mechanisms.

Posttranscriptional Controls

Although controls on the initiation of gene transcription are the predominant form of regulation for most genes, other controls can act later in the pathway from RNA to protein to modulate the amount of gene product that is made. Although these **posttranscriptional controls,** which operate after RNA polymerase has bound to the gene's promoter and begun RNA synthesis, are less common than *transcriptional control,* for many genes they are crucial. It seems that every step in gene expression that could be controlled in principle is likely to be regulated under some circumstances for some genes.

We consider the varieties of posttranscriptional regulation in temporal order, according to the sequence of events that might be experienced by an RNA molecule after its transcription has begun (Figure 9–72).

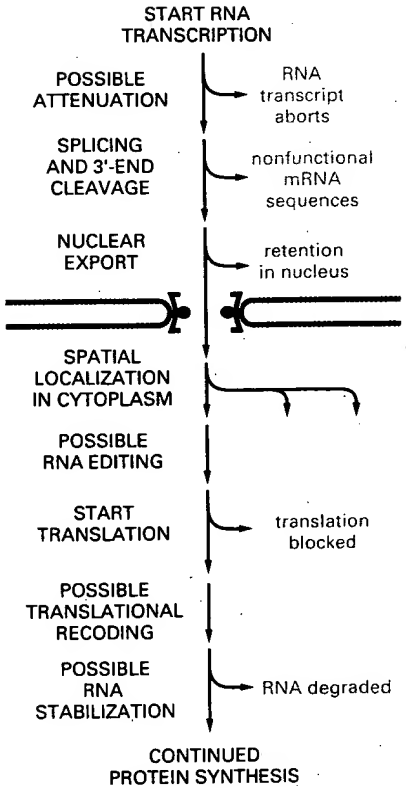

Figure 9–72 **Possible posttranscripti nal controls on gene expression.** Only a few of these controls are likely to be used for any one gene.